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10/723,164	11/26/2003	Stephan R. Targan	025663-001201US	8299
20350 7590 04/30/2010 TOWNSEND AND TOWNSEND AND CREW, LLP TWO EMBARCADERO CENTER EIGHTH FLOOR SAN FRANCISCO, CA 94111-3834				
EXAMINER				
ROONEY, NORA MAUREEN				
ART UNIT		PAPER NUMBER		
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/723,164

**Applicant(s)**

TARGAN ET AL.

**Examiner**

NORA M. ROONEY

**Art Unit**

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 22 December 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 37-45 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 37-45 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/22)
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date: \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_
- Paper No(s)/Mail Date 12/22/2009

**DETAILED ACTION**

1. Applicant's amendment filed on 12/22/2009 is acknowledged.
2. Newly added claims 37-45 are now pending and under consideration as they read on a method of determining a risk of having or developing a clinical subtype of Crohn's disease in a subject having Crohn's disease.
3. Applicant's IDS document filed on 12/22/2009 is acknowledged.
4. The following new grounds of rejection are necessitated by the amendment filed 12/22/2009.

***Double Patenting***

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

*Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 37-45 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 7,662,569 (PTO-892; Reference A). Although the conflicting claims are not identical, they are not patentably distinct from each other because Claims 1-14 of U.S. patent 7,662,569 are directed to : a method for determining the likelihood of being susceptible to a fibrostenotic subtype of Crohn's disease characterized by small bowel involvement in a subject having Crohn's disease, said method comprising: (a) obtaining a sample from the subject; (b) contacting the sample from the subject with an antigen or fragment thereof specifically reactive with IgA anti-I2 antibodies; and (c) assaying for the level of IgA anti-I2 antibodies in said sample by detecting specific binding of said antigen or fragment thereof, wherein a high level of said IgA anti-I2 antibodies is indicative of an increased likelihood of said fibrostenotic subtype of Crohn's disease characterized by small bowel involvement, further comprising determining the presence or absence of a NOD2 variant

selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8 in the subject, wherein a high level of IgA anti-I2 antibodies and the presence of said NOD2 variant in the subject indicates an increased likelihood of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery, and further comprising determining the level of anti-Saccharomyces cerevisiae antibodies (ASCA) in the subject, comprising obtaining a sample from the subject; contacting the sample from the subject with an antigen or fragment thereof specifically reactive with ASCA; and assaying for the level of ASCA in said sample by detecting specific binding of said antigen or fragment thereof, wherein a high level of said IgA anti-I2 antibodies and a high level of said ASCA in the subject indicates an increased likelihood of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery; and instant claims 37-45 are directed to a method of determining a risk of having or developing a clinical subtype of Crohn's disease in a subject having Crohn's disease, said clinical subtype characterized by fibrostenosis or the need for small bowel surgery, said method comprising: (a) obtaining a sample from the subject; (b) contacting the sample from the subject with an antigen or fragment thereof specifically reactive with IgA anti-I2 antibodies; and (c) determining the presence and magnitude of IgA anti-I2 antibody response in the subject, wherein a greater magnitude of IgA anti-I2 antibody response indicates a greater risk of having or developing said clinical subtype characterized by fibrostenosis or the need for small bowel surgery, further comprising determining the presence or absence of a NOD2 variant selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8 in the subject, wherein a greater magnitude of IgA anti-I2 antibodies and the presence of said NOD2

variant in the subject indicates a greater risk of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery, further comprising determining the magnitude of anti-Saccharomyces cerevisiae antibodies (ASCA) in the subject, comprising obtaining a sample from the subject; contacting the sample from the subject with an antigen or fragment thereof specifically reactive with ASCA; and assaying for the level of ASCA in said sample by detecting specific binding of said antigen or fragment thereof, wherein a greater magnitude of said IgA anti-I2 antibodies and a greater magnitude of said ASCA in the subject indicates a greater risk of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery and further comprising determining the presence or absence of IgA anti-OmpC antibodies.

7. Claims 37-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of copending Application No. 12/196,505. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claims 1-8 of 12/196,505 are directed to : a method of diagnosing susceptibility to a fibrostenotic subtype of Crohn's Disease in an individual, comprising: determining the presence or absence of at least one risk variant at the NOD2 locus in the individual, and determining the presence or absence of at least one risk serological marker in the individual; wherein the presence of at least one risk variant and at least one risk serological marker is diagnostic of susceptibility to fibrostenotic subtype of Crohn's Disease, wherein said risk serological markers are selected from the group consisting of oligomannan (ASCA), Cbir, OmpC, and I2, or any combination thereof, wherein the presence of four of said risk serological markers presents a greater susceptibility than the presence of three or two or one or

none of said risk serological markers, and the presence of three of said risk serological markers presents a greater susceptibility than the presence of two or one or none of said risk serological markers but less than the presence of four risk serological markers, and the presence of two of said risk serological markers presents a greater susceptibility than the presence of one or none of said risk serological markers but less than the presence of four or three risk serological markers, and the presence of one of said risk serological markers presents a greater susceptibility than the presence of none of said risk serological markers but less than the presence of four or three or two of said risk serological markers; and instant claims 37-45 are directed to a method of determining a risk of having or developing a clinical subtype of Crohn's disease in a subject having Crohn's disease, said clinical subtype characterized by fibrostenosis or the need for small bowel surgery, said method comprising: (a) obtaining a sample from the subject; (b) contacting the sample from the subject with an antigen or fragment thereof specifically reactive with IgA anti-I2 antibodies; and (c) determining the presence and magnitude of IgA anti-I2 antibody response in the subject, wherein a greater magnitude of IgA anti-I2 antibody response indicates a greater risk of having or developing said clinical subtype characterized by fibrostenosis or the need for small bowel surgery, further comprising determining the presence or absence of a NOD2 variant selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8 in the subject, wherein a greater magnitude of IgA anti-I2 antibodies and the presence of said NOD2 variant in the subject indicates a greater risk of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery, further comprising determining the magnitude of anti-Saccharomyces cerevisiae antibodies (ASCA) in the subject, comprising obtaining a sample from

the subject; contacting the sample from the subject with an antigen or fragment thereof specifically reactive with ASCA; and assaying for the level of ASCA in said sample by detecting specific binding of said antigen or fragment thereof, wherein a greater magnitude of said IgA anti-I2 antibodies and a greater magnitude of said ASCA in the subject indicates a greater risk of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery and further comprising determining the presence or absence of IgA anti-OmpC antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 37-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of copending Application No. 12/527,376. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claims 1-9 of 12/527,376 are directed to: a method of diagnosing susceptibility to Crohn's Disease in an individual, comprising: determining the presence or absence of at least one risk variant at the NOD2 locus selected from the group consisting of R702W, G908R and 1007fs, and determining the presence or absence of at least one risk serological marker, wherein the presence of at least one risk variant and at least one risk serological marker is diagnostic of susceptibility to Crohn's Disease, wherein the presence of three of said risk variants at the NOD2 locus presents a greater susceptibility than the presence of two, one or none of said risk variants at the NOD2 locus, and the presence of two of said risk variants at the NOD2 locus presents a greater susceptibility than the presence of one or none of said risk variants at the NOD2 locus but less than the presence of three risk variants at the NOD2



locus, and the presence of one of said risk variants at the NOD2 locus presents a greater susceptibility than the presence of none of said risk variants at the NOD2 locus but less than the presence of three or two of said risk variants at the NOD2 locus, wherein said risk serological markers are selected from the group consisting of ASCA, I2, OmpC and Cbir, wherein the presence of four of said risk serological markers presents a greater susceptibility than the presence of three or two or one or none of said risk serological markers, and the presence of three of said risk serological markers presents a greater susceptibility than the presence of two or one or none of said risk serological markers but less than the presence of four risk serological markers, and the presence of two of said risk serological markers presents a greater susceptibility than the presence of one or none of said risk serological markers but less than the presence of four or three risk serological markers, and the presence of one of said risk serological markers presents a greater susceptibility than the presence of none of said risk serological markers but less than the presence of four or three or two of said risk serological markers; and instant claims 37-45 are directed to a method of determining a risk of having or developing a clinical subtype of Crohn's disease in a subject having Crohn's disease, said clinical subtype characterized by fibrostenosis or the need for small bowel surgery, said method comprising: (a) obtaining a sample from the subject; (b) contacting the sample from the subject with an antigen or fragment thereof specifically reactive with IgA anti-I2 antibodies; and (c) determining the presence and magnitude of IgA anti-I2 antibody response in the subject, wherein a greater magnitude of IgA anti-I2 antibody response indicates a greater risk of having or developing said clinical subtype characterized by fibrostenosis or the need for small bowel surgery, further comprising determining the presence or absence of a NOD2 variant selected from the group consisting of

SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8 in the subject, wherein a greater magnitude of IgA anti-I2 antibodies and the presence of said NOD2 variant in the subject indicates a greater risk of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery, further comprising determining the magnitude of anti-Saccharomyces cerevisiae antibodies (ASCA) in the subject, comprising obtaining a sample from the subject; contacting the sample from the subject with an antigen or fragment thereof specifically reactive with ASCA; and assaying for the level of ASCA in said sample by detecting specific binding of said antigen or fragment thereof, wherein a greater magnitude of said IgA anti-I2 antibodies and a greater magnitude of said ASCA in the subject indicates a greater risk of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery and further comprising determining the presence or absence of IgA anti-OmpC antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Claims 37-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9-12, 17-21 and 23-26 of copending Application No. 12/529,106. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claims 9-12 and 17-21 and 23-26 of 12/529,106 are directed to: a method of diagnosing susceptibility to a subtype of Crohn's Disease in a child, comprising: determining the presence or absence of a high immune reactivity relative to a healthy individual for at least one risk serological marker, selected from the group consisting of Cbirl, OmpC, ASCA, 12, and pANCA, wherein the presence of a high immune reactivity

relative to a healthy individual to at least one risk serological marker is diagnostic of susceptibility to the subtype of Crohn's Disease in a child, wherein the subtype of Crohn's Disease in a child comprises an aggressive complicating phenotype, wherein a high immune reactivity comprises a high magnitude of expression for the risk serological marker, wherein the presence of four of said risk serological markers presents a greater susceptibility than the presence of three, two, one or none of said risk serological markers, and the presence of three of said risk serological markers presents a greater susceptibility than the presence of two, one or none of said risk serological markers but less than the presence of four of said risk serological markers, and the presence of two of said risk serological markers presents a greater susceptibility than the presence of one or none of said risk serological markers but less than the presence of four or three of said risk serological markers, and the presence of one of said risk serological markers presents a greater susceptibility than the presence of none of said risk serological markers but less than the presence of four or three or two of said risk serological markers. ; a method of determining the prognosis of Crohn's Disease in an individual, comprising: determining the presence or absence of a high immune reactivity relative to a healthy individual for at least one risk serological marker, selected from the group consisting of Cbirl, OmpC, ASCA, and pANCA, wherein the presence of a high immune reactivity relative to a healthy individual to at least one risk serological marker is indicative of a prognosis of an aggressive form of Crohn's Disease, wherein the prognosis of an aggressive form of Crohn's Disease further comprises a rapid complicating internal penetrating and/or fibrostenosing disease phenotype; and a method of determining the prognosis of Crohn's Disease in a pediatric subject, comprising: determining the presence or absence of a high immune reactivity of Cbirl, OmpC, ASCA, and

pANCA in the pediatric subject relative to a child who has and maintains a non-aggressive form of Crohn's Disease, wherein the presence of the high immune reactivity relative to a child who has and maintains a non-aggressive form of Crohn's Disease is indicative of a prognosis of an aggressive form of Crohn's Disease in the pediatric subject, wherein the aggressive form of Crohn's Disease further comprises a rapid complicating internal penetrating and/or stricturing disease phenotype; and a method of determining the prognosis of Crohn's Disease in a subject, comprising: determining the presence or absence of a high immune reactivity in the subject relative to an individual who has and maintains a non-aggressive form of Crohn's Disease for at least one risk serological marker, selected from the group consisting of Cbirl, OmpC, ASCA, and pANCA, wherein the presence of the high immune reactivity relative to an individual who has and maintains a non-aggressive form of Crohn's Disease is indicative of a prognosis of an aggressive form of Crohn's Disease, wherein the aggressive form of Crohn's Disease further comprises a rapid complicating internal penetrating and/or fibrostenosing disease phenotype; and instant claims 37-45 are directed to a method of determining a risk of having or developing a clinical subtype of Crohn's disease in a subject having Crohn's disease, said clinical subtype characterized by fibrostenosis or the need for small bowel surgery, said method comprising: (a) obtaining a sample from the subject; (b) contacting the sample from the subject with an antigen or fragment thereof specifically reactive with IgA anti-I2 antibodies; and (c) determining the presence and magnitude of IgA anti-I2 antibody response in the subject, wherein a greater magnitude of IgA anti-I2 antibody response indicates a greater risk of having or developing said clinical subtype characterized by fibrostenosis or the need for small bowel surgery, further comprising determining the presence or absence of a NOD2 variant selected from the group

consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8 in the subject, wherein a greater magnitude of IgA anti-I2 antibodies and the presence of said NOD2 variant in the subject indicates a greater risk of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery, further comprising determining the magnitude of anti-Saccharomyces cerevisiae antibodies (ASCA) in the subject, comprising obtaining a sample from the subject; contacting the sample from the subject with an antigen or fragment thereof specifically reactive with ASCA; and assaying for the level of ASCA in said sample by detecting specific binding of said antigen or fragment thereof, wherein a greater magnitude of said IgA anti-I2 antibodies and a greater magnitude of said ASCA in the subject indicates a greater risk of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery and further comprising determining the presence or absence of IgA anti-OmpC antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Claims 37-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of copending Application No. 12/645,394. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claims 1-24 of Application 12/645,394 are directed to: a method of diagnosing or predicting susceptibility to a fibrostenotic subtype of Crohn's disease in a subject having Crohn's disease, comprising determining the presence or absence of IgA anti-I2 antibodies in the subject, wherein the presence of said IgA anti-I2 antibodies indicates that the subject has said fibrostenotic subtype of crohn's disease, further comprising determining the

presence or absence in the subject of one or more fibrostenotic markers selected from a NOD2 variant, *anti-Saccharomyces cerevisiae* antibodies (ASCA), and anti-OmpC antibodies, wherein the presence of said IgA anti-I2 antibodies or the presence of one of said one or more fibrostenotic markers each independently indicates that the subject has said fibrostenotic subtype of Crohn's disease, wherein the combined presence of IgA anti-I2 antibodies, said NOD2 variant, and said ASCA in the subject indicates that the subject has said fibrostenotic subtype of Crohn's disease, said clinical subtype of Crohn's disease is characterized by the need for small bowel surgery, further comprising determining the presence or absence in the subject of one or more markers selected from a NOD2 variant, *anti-Saccharomyces cerevisiae* antibodies (ASCA), IgA anti- OmpC antibodies, and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA); and phenotype; and instant claims 37-45 are directed to a method of determining a risk of having or developing a clinical subtype of Crohn's disease in a subject having Crohn's disease, said clinical subtype characterized by fibrostenosis or the need for small bowel surgery, said method comprising: (a) obtaining a sample from the subject; (b) contacting the sample from the subject with an antigen or fragment thereof specifically reactive with IgA anti-I2 antibodies; and (c) determining the presence and magnitude of IgA anti-I2 antibody response in the subject, wherein a greater magnitude of IgA anti-I2 antibody response indicates a greater risk of having or developing said clinical subtype characterized by fibrostenosis or the need for small bowel surgery, further comprising determining the presence or absence of a NOD2 variant selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8 in the subject, wherein a greater magnitude of IgA anti-I2 antibodies and the presence of said NOD2 variant in the subject indicates a greater risk of an

aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery, further comprising determining the magnitude of anti-Saccharomyces cerevisiae antibodies (ASCA) in the subject, comprising obtaining a sample from the subject; contacting the sample from the subject with an antigen or fragment thereof specifically reactive with ASCA; and assaying for the level of ASCA in said sample by detecting specific binding of said antigen or fragment thereof, wherein a greater magnitude of said IgA anti-I2 antibodies and a greater magnitude of said ASCA in the subject indicates a greater risk of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery and further comprising determining the presence or absence of IgA anti-OmpC antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. It is again noted that the effective priority date for the instant claims is the filing date of the instant specification because there is insufficient support in the 10/413,501 priority document's specification for the invention as claimed. In particular, there is insufficient support in the priority document for determining the magnitude of the markers and for determining the risk of having or developing a clinical subtype of Crohn's disease based on measuring anti-I2 antibodies, anti-Saccharomyces cerevisiae antibodies and IgA anti-OmpC antibodies.

***Claim Rejections - 35 USC § 102***

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. Claims 37-44 are rejected under 35 U.S.C. 102(a) as being anticipated by Mow et al. (IDS filed on 11/03/2004; Reference 21) as evidenced by the specification on page 4, line 24 to page 5, line 14.

Mow et al. teaches measuring anti-I2 antibodies and anti-Saccharomyces cerevisiae antibodies (ASCA) in the serum of Crohn's disease patients by ELISA (contacting the sample from the subject with an antigen or fragment thereof specifically reactive with IgA anti-I2 antibodies, ASCA contacting a sample from the subject with an I2/ASCA antigen under conditions suitable to form a first complex of I2/ASCA antigen and antibody against said I2/ASCA antigen; contacting said first complex with a labeled secondary antibody to form a second complex; and detecting a level of said second complex, wherein a high level of said second complex indicates a high level of said IgA anti-I2 /ASCA antibodies) and genotyping for the three CD-associated variants of the NOD2 gene, R702W, G908R, 1007fs and determining the risk of having or developing fibrostenosis or the need for small bowel surgery. The reference found that patients expressing I2 were significantly more likely to have fibrostenosing CD and to require small bowel surgery in addition to anti-Saccharomyces cerevisiae antibodies (ASCA) and CD-associated variants of the NOD2 gene, R702W, G908R, 1007fs, which were known to be



associated with fibrostenosing CD. Patients with all three showed the greatest risk of having fibrostenosing CD compared with patients having one, two or no markers.

Claims 39-40 and 43-44 are included in this rejection because SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8 are the CD-associated variants of the NOD2 gene, R702W, G908R, 1007fs as evidenced by the specification on page 4, line 24 to page 5, line 14.

The recitation of "with an odds ratio of at least 6" in claims 40 and 42 and "with an odds ratio of at least 9" in claim 44 is inherent. The same method steps are being performed in the same patient samples for the same result. So, the risk is inherently having an odds ratio of "at least 6" or "at least 9."

The reference teachings anticipate the claimed invention.

***Claim Rejections - 35 USC § 103***

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. Claims 37-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Targan et al. (PTO-892 mailed on 01/29/2007, Reference U) in view of Vasiliauskas et al. (Reference 30,

IDS filed on 11/03/2004), Landers et al. (Reference 17, IDS filed on 11/03/2004) and U.S. Patent Application Publication 2004/0053263 (PTO-892; Reference B).

Targan et al., teaches detecting the magnitude (predominant reactivity was defined as a high level of a single antibody) of anti-I2, ASCA and anti-OmpC IgA molecules in patients with ileal or illeal with right sided colonic Crohn's disease by ELISA. The results were correlated with antibiotic induced clinical remission (a clinical subtype). The results showed that patients having anti-I2, ASCA or anti-OmpC IgA molecules were more likely to achieve antibiotic-induced clinical remission (In particular, abstract).

The claimed invention differs from the prior art by the recitation of "characterized by fibrostenosis or the need for small bowel surgery" and "wherein a greater magnitude of IgA anti-I2 antibody response indicates a greater risk of having or developing said clinical subtype characterized by fibrostenosis or the need for small bowel surgery" of claim 37; "further comprising determining the presence or absence of a NOD2 variant selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8 in the subject, wherein a greater magnitude of IgA anti-I2 antibodies and the presence of said NOD2 variant in the subject indicates a greater risk of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery" of claim 39; "wherein the combined greater magnitude of said IgA anti-I2 antibodies and the presence of said NOD2 variant in the subject indicates a greater risk of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery with an odds ratio of at least 6" of claim 40; "wherein a greater magnitude of said IgA anti-I2 antibodies and a greater magnitude of said ASCA in the subject indicates a greater risk of an aggressive form of said fibrostenotic

subtype of Crohn's disease requiring small bowel surgery" of claim 41; "wherein the combined greater magnitude of said IgA anti-I2 antibodies and said ASCA in the subject indicates a greater risk of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery with an odds ratio of at least 6" of claim 42; "wherein the combined greater magnitude of IgA anti-I2 antibodies and said ASCA and the presence of said NOD2 variant in the subject indicates the greatest risk for an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery" of claim 43; and "the combined greater magnitude of said IgA anti-I2 antibodies and said ASCA and the presence of said NOD2 variant in the subject indicates a greater risk of an aggressive form of said fibrostenotic subtype of Crohn's disease requiring small bowel surgery with an odds ratio of at least 9" of claim 44.

Vasiliauskas et al. teaches that numerous attempts have been made to characterize CD patients into uniform subgroups to better understand and predict clinical course and responses to medical and surgical interventions, particularly by serum immune markers and using selective expression of markers was demonstrated as a complementary approach for identification of immunologically and clinically homogeneous subgroups (In particular, first two paragraphs on page 487, page 493 first paragraph of the 'Discussion'). The reference teaches detecting the magnitude of ASCA and ANCA antibodies as a tool to stratify Crohn's disease into immunologically homogeneous subgroups with distinct clinical characteristics including fibrostenosis, internal perforating disease and the need for small bowel surgery. ('Assessment of clinical characteristics' section pages 488-489, paragraph spanning 490-491, section spanning pages 491-493). The antibody levels were normalized and compared and statistical analysis was performed. The reference also teaches that a high magnitude of two of the markers indicates a

first risk of having or developing the clinical subtype of Crohn's disease, a high magnitude of one of the markers indicates a second risk of having or developing said clinical subtype of Crohn's disease, and the absence of a high magnitude of the markers indicates a third risk of having or developing said clinical subtype of Crohn's disease (In particular, paragraph spanning page 491 to last paragraph on page 492, discussion, whole document). Marker magnitude predicted Crohn's disease clinical characteristics and the reference suggests using further immune markers to better characterize and stratify disease subgroups (In particular, abstract, page 493, first paragraph of discussion and throughout results, page 494, last paragraph).

Landers et al. teaches detecting the magnitude of OmpC, ASCA and anti-I2 antibodies to determine the relationship of serum activity to these antigens in a clinical cohort a clinical subtype (loss of tolerance to microbial antigens). The markers were measured and quartile and cluster analysis was performed to determine the relationship between the marker antibodies in the Crohn's disease cohort (In particular, Figure 2). A number was assigned to each quartile and the sum of the quartiles was correlated to reactivity (In particular, paragraph spanning pages 693-694). The reference also teaches that a high magnitude of the three markers relative to levels found in individuals who do not have Crohn's disease indicates a first risk of having or developing the clinical subtype of Crohn's disease, a high magnitude of two of the markers relative to levels found in individuals who do not have Crohn's disease indicates a second risk of having or developing the clinical subtype of Crohn's disease, a high magnitude of one of the three markers relative to levels found in individuals who do not have Crohn's disease indicates a third risk of having or developing said clinical subtype of Crohn's disease, and the absence of a

high magnitude of the three markers relative to levels found in individuals who do not have Crohn's disease indicates a fourth risk of having or developing said clinical subtype of Crohn's disease (In particular, Table 1, Figures 2-7, 'Discussion' section).

U.S. Patent Publication 2004/0053263 teaches the mutation in NOD2 of SEQ ID NOs: 1, 2, 3, 4, 5 and 6 (100% identical over length and sequence to instant SEQ ID NOs:3, 4, 5, 6, 7 and 8, respectively) are associated with fibrostenosing disease in Crohn's disease patients. (In particular, abstract, SEQ ID NOs 1-6; whole document).

It would have been obvious to a person of ordinary skill in the art at the time the invention to combine the teachings of Targan, Landers and Vasiliauskas because all three references are directed to measuring antibodies to bacteria associated antigens to stratify Crohn's Disease patients into clinical subtypes. It would also be obvious to analyze the data to determine risk of developing the clinical subtype based upon the magnitude of the antibodies to bacteria associated antigens. It would be obvious to determine the risk of having or developing the disease based upon the magnitude of three, two, one and no detectable antibodies to bacteria associated antigens. It would be obvious to analyze the data statistically and based on the teaching of Landers et al., it would be obvious to determining the odds ratio to correlate the data to a clinical subtype. It would have been obvious to perform the method of determining the correlation of Crohn's disease markers anti-I2, ASCA and anti-OmpC IgA to any of the clinical outcomes of Targan et al. and Vasiliauskas et al. to obtain the claimed invention particularly since Vasiliauskas et al. teaches that numerous attempts have been made to characterize CD

patients into uniform subgroups to better understand and predict clinical course and responses to medical and surgical interventions, particularly by serum immune markers and that stratification based on CD behavior has been widely studied and reported. It would also have been obvious to one of ordinary skill in the art to determine the presence of a NOD2 variant as taught by U.S. Patent Publication 2004/0053263 in the method of Landers et al. because the NOD2 variant had been shown to be associated with fibrostenosing disease Crohn's disease. Therefore, the combined method of all of the references would determine Crohn's disease patients with a fibrostenotic subtype. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. No claim is allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Nora M. Rooney

Patent Examiner

Technology Center 1600

/Nora M Rooney/

Examiner, Art Unit 1644